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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FOLEY & LARDNER LLP
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,791	CHIEN ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19,23,24 and 32-34* is/are pending in the application.

4a) Of the above claim(s) *25-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19,23,24 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/10/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment received on 10/03/05 has been entered. Claims 20-22 have been cancelled. Claims 18-19 and 23-34 have been amended. New claims 32-34 have been added. Claims 25-31 are withdrawn from further consideration as being drawn to a nonelected invention.

2. Claims 18-19 and 23-34 are pending.

3. Applicant's claims amendments and provisional election of species with traverse of claims 18-19, 23-24 and 32-34 in the reply on October 3, 2005 is acknowledged. Claims 18-19, 23-24 and 32-34 are under current consideration in light of the election of dominant negative phospholamban The traversal is on the grounds that: (i) election between impact on cardiac contractility and cardiac relaxation of cardiac muscle are physiologically linked and one necessarily follows the other. Examiner agrees and therefore that cardiac contractility and cardiac relaxation are physiologically linked and therefore will be examined together; (ii) election between expression constructs, applicants elected dominant-negative (dn) PLB molecules versus the antisense molecules. Applicants argue that any further restriction between the dnPLB molecules disclosed is not warranted. Applicants also argue that each dn PLB molecule disclosed disrupts the physiological interaction between endogenous PLB and SERCA2, thereby modifying the set point of in vivo contractility and relaxation targeted by the invention and it is this effect, rather than the particular structure of the molecules used to accomplish it, that is presently claimed, therefore, as all of the dnPLB molecules disclosed and claimed accomplish the claimed goals of the invention. However, examiner disagrees that all dnPLB molecules exert the same effect on the set point of in vivo contractility and relaxation targeted

by the invention because each dnPLB molecule has distinct structure, function and mechanism of action and even though they may be based on the same concept, they are patentably distinct, will require separate search in the art and both search and examination; (iii) election between expression vectors and promoter, applicant elected viral vectors and withdrew promoter and vector election requirement. Applicants further argue that the characteristics of those vectors and the advantages and disadvantages presented by each, are well known and to varying degrees, such vectors can be reasonably expected to produce expression of the dnPLB molecules disclosed, to accomplish the disruption between PLB and SERCA2's interaction by the claimed invention and it is this effect rather than the particular structure of the molecules used to accomplish it, therefore, election among particular vectors that may all be used to that end should not be required. However, examiner disagrees that all expression vectors can be reasonably expected to produce expression of dnPLB molecules to varying degrees to accomplish disruption between PLB and SERCA2's interaction, because even though they may be based on the same concept, they are patentably distinct, will require separate search in the art and both search and examination. Accordingly, the applicants traverse the restriction requirement. The applicants expressly reserve the right under USC 35 &121 to file a divisional application during the pendency of this application. The requirement is still deemed proper and is therefore made FINAL. Thus, claims 25-31 are withdrawn form further consideration as being drawn to a nonelected invention. Applicants timely traverse the restriction (election) requirement in the reply filed on October 3, 2005.

Oath/Declaration

4. Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Priority

5. It is noted that this application appears to claim subject matter disclosed in prior divisional application of U.S. Patent Application Serial No. 09/-------, however, sentence in line 6 of the paragraph is missing the appropriate application No. Appropriate correction is required. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all non provisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or

119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-19, 23-24 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention encompasses a method of treating any condition associated with the loss of cardiac muscle contractility comprising delivering an expression construct to cardiac myocytes wherein the expression construct provides an expressible polynucleotide encoding a dominant-negative phospholamban (dnPLB) molecule wherein further expression of the polynucleotide accelerates SERCA2 mediated calcium ion transport in the myocytes to improve cardiac muscle contractility in vitro or in vivo (see claim 1). Dependent claims 19 and 24 limit the construct to any viral vector. Dependent claim 23 limits the dnPLB molecule to containing a single or double point mutation in Domain Ia, the effect of which is to diminish the inhibitory activity of PLB on SERCA2. Dependent claim 32 limits the mutation to a point mutation consisting of R14E, S16N, S16E or K3E/R14E. Dependent claim 33 limits the single or double point mutation in Domain II, the effect of which is to diminish the inhibitory activity of PLB on SERCA2 and dependent claim 34 further limits the point mutation consisting of V49E.

In determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are; the breadth of the claims, the nature of the invention, the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)). Furthermore, USPTO does not have laboratory

facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

These factors are analyzed, in turn, and demonstrate that one of ordinary skill in the art will need to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

In the instant application, the factors set forth are; (a) the breadth of the claims, the nature of the invention and the unpredictability for practicing said method of treating any condition associated with the loss of cardiac muscle contractility by delivering any viral vector encoding for dominant-negative phospholamban (dnPLB) molecule wherein further expression of the polynucleotide accelerates SERCA2 mediated calcium ion transport in the myocytes to improve cardiac muscle contractility in vivo or in vitro; (b) the amount of sufficient guidance provided for practicing claimed method; (c) a working example for practicing claimed method.

The claims are directed to methods of treating any condition associated with the loss of cardiac muscle contractility comprising delivering an expression construct to cardiac myocytes wherein the expression construct provides an expressible polynucleotide encoding a dominant-negative phospholamban (dnPLB) molecule wherein further expression of the polynucleotide accelerates SERCA2 mediated calcium ion transport in the myocytes to improve cardiac muscle contractility and clearly fall into the realm of gene therapy (see claim 1). Dependent claims 19 and 24 limit the construct to any viral vector. Dependent claim 23 limits the dnPLB molecule to containing a single or double point mutation in Domain Ia, the effect of which is to diminish the

inhibitory activity of PLB on SERCA2. Dependent claim 32 limits the mutation to a point mutation consisting of R14E, S16N, S16E or K3E/R14E. Dependent claim 33 limits the single or double point mutation in Domain II, the effect of which is to diminish the inhibitory activity of PLB on SERCA2 and dependent claim 34 further limits the point mutation consisting of V49E. Because these claims encompass a wide range of dnPLB nucleic acid conditions sufficient for its expression to accelerate SERCA2 mediated calcium ion transport in the treated cardiac myocytes to improve cardiac muscle contractility in vitro or in vivo in any subject including humans and phenotypes associated with it, the detail of the disclosure provided by the applicant, in view of the prior art, must encompass a wide knowledge, so that one of skill in the art, at the time of the invention, would be able to practice the invention as claimed by the applicant, without undue burden being imposed on the artisan. As discussed below, this burden has not been met because it would require undue experimentation to treat any condition associated with loss of cardiac muscle contractility utilizing claimed method.

Claimed method encompasses any route of administration, any site of the heart and any viral vector encoding for any of said dominant-negative phospholamban (dnPLB) molecules. However, the specification as filed does not provide sufficient guidance to practice claimed method to commensurate with the full scope of the claims and an artisan of skill would have required extensive experimentation to practice the claimed invention commensurate with the full scope of claims and such experimentation will be undue since the art of gene therapy is unpredictable. The role of said dnPLB's viral vectors in treating a condition associated with the loss of cardiac muscle contractility in vivo varies depending on the route of administration, the dose of the vector and cardiac muscle tissue target specificity and the specification does not provide sufficient guidance to address these issues for an artisan to practice the claimed

invention. The specification merely describes that PLB/SERCA2a interaction may be a potential therapeutic target for the treatment of heart failure (p 5, lines 7-10). The specification also describes that the need remains for methods for the inhibition of PLB through the use of mutants to manipulate the PLB/SERCA2a interaction in cardiac myocytes as well a transport means for these mutants of PLB to cross sarcoplasmic reticulum (SR) membrane barriers into the cytoplasm of cardiac myocytes for the treatment of cardiac disease and heart failure (p 5, last line and p 6, lines 1-5). The specification in figure 1 illustrates diagrammatically a working model for the role of the PLB/SERCA2a interaction in the progression of heart failure. The specification discloses the construction of recombinant human adenovirus containing wild type, single point mutations of PLB, V49A, or E2A or R14E or S16N or double point mutations of PLB K3E/R14 of PLB gene (specification p 17 lines 11-15). Specification discloses that, murine cardiac myocytes overexpressing adenovirus mediated single point mutation V49A PLB transgene, exhibit an increase in contractility, while myocytes overexpressing wild type PLB transgene exhibit a decrease in contractility when compared to non-infected myocytes as documented in figure 5, (specification p 17, lines 17-25). The specification also discloses that from these results it can be concluded that the feasibility and utility of interfering with the interaction between the SERCA2a and the PLB is clearly documented and the PLB/SERCA2a interaction appears to be the rate limiting step for establishing the set point of basal cardiac contractility and relaxation in vivo, and the disruption of this interaction can thereby short circuit the β-adrenergic pathway (specification p 17, lines 25-28). In addition, specification discloses that, neonatal or adult rat cardiomyocytes infected with the recombinant adenovirus transgene K3E/R14E show a decrease in the concentration of calcium needed by SERCA2a for the same activity compared with the non-transgene control, indicating a stimulation of SERCA2a activity (specification, p 19, lines 6- 12, figure 7). The specification also discloses efficient in vivo

cardiac gene transfer was performed by injecting wild type and single point mutation V49A PLB adenovirus vectors into 1 day old neonatal mouse heart (specification p 28, lines 1-15). Cardiac myocytes were isolated 4 weeks after injection into the mouse hearts and cell shortening was measured. Cardiac myocytes harboring the mutant transgenes were identified by co-transfection of adenoviral vectors expressing GFP as marker (specification p 28, lines 1-15, example 3). In addition, adult rabbit myocytes infected with the adenoviral transgenes of Lac Z gene or wild type PLB or double point mutation K3E/R14E PLB transgene, K3E/R14E infected myocytes display an enhanced fractional shortening, which suggests an increase in SR loads of calcium due to the enhancement of SERCA2a activity (specification, p 22, lines 19-23).

However, these results do not indicate or provide evidence that when any viral vector or any adenoviral vector encoding for any of said dnPLB transgenes is administered by any route at any dose to a patient or a subject suffering from a condition associated with loss of cardiac muscle contractility it would result in acceleration of SERCA2a mediated calcium ion transport of cardiac myocytes which in turn will result in improved cardiac muscle contractility compared to patients or subjects treated with wild type dnPLB viral vector. At the time of the instant invention, the art teaches that adenoviral vectors carrying cDNA for either wild type PLB or beta-galactosidase or modified green fluorescence protein (EGFP) two days after infection via catheter based technique, rat hearts transduced with Ad.PLB had lower peak left ventricular pressure compared with uninfected or Ad.beta-galactosidase (Hajjar et al, Proc Natl Acad Sci, 95: 5251-5256, April 1998) (p 5251 abstract). However, the authors further note: "Eventhough our delivery method was specifically targeted to the heart we found expression of the reporter transgene in other tissues in the body, such as lung liver but not in aorta by using histochemical staining. Other investigators have found extracardiac transgene expression following in vivo injection of adenovirus into the heart when using a nonspecific promoter. The use of tissue

specific promoters may obviate this problem in the future." (p 5155, 2nd column, 3rd paragraph). Furthermore, the authors note: "However, adenoviruses have significant disadvantages that include the transient nature of overexpression of desired gene and the immune/inflammatory response they produce and which was also present in our infected hearts. These shortcomings of the first generation adenoviruses limit their use in animal models over prolonged period of time." (p 5256, 1st column, 2nd paragraph). The issue of cell specific promoter is also supported by the art of Inesi et al, (Am J Physiol Cell Physiol, 274(3): C645-C653, March 1998) (abstract) where they described cell-specific promoter in adenovirus vector for transgenic expression of SERCA1 ATPase in cardiac myocytes. Therefore, it is not clear as to how an artisan will use claimed adenoviral vectors in treating any condition associated with loss of cardiac muscle contractility by expressing any or all dnPLB transgenes in the desired cardiac myocytes in vivo without non specific targeting in other cell types or tissues in any animal or subject. In addition, the specification discloses that adult rabbit myocytes infected with the adenoviral transgenes of Lac Z gene or wild type PLB or double point mutation K3E/R14E PLB transgene, K3E/R14E infected myocytes display an enhanced fractional shortening, which suggests an increase in SR loads of calcium due to the enhancement of SERCA2a activity (specification, p 22, lines 19-23). However, these results in vitro can not be extrapolated in vivo in any animal or human for treating a condition associated with loss of cardiac muscle contractility.

Next, the art of gene delivery is unpredictable. Numerous factors complicate the gene delivery art which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction taken up by he target population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the

mRNA produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the various viral vectors used and the protein being produced. In the instant case, it is claimed the use of any viral vector for practicing claimed method. While progress has been made in recent years for gene transfer, in vivo, vector targeting to desired organs continuous to be unpredictable and inefficient. This is supported by numerous teachings in the art. Prasad et al, (Biochemical and Biophysical Research Communications, 322: 1192-1203, 2004) eve after filing of the instant application noted that gene targeting studies of SERCA isoforms and plasma membrane (PMCA) isoforms have confirmed some of the general functions proposed for these pumps, but have also revealed some unexpected phenotypes. These include squamous cell cancer and plasticity in the regulation of calcium-mediated exocytosis in SERCA2 heterozygous mutant mice (p 1192, abstract). Romano et al, (The Oncologist, 3: 225-236, 1998) while reviewing the state of the art of gene transfer technology in therapy, at the time of the instant invention noted, "The standpoint of gene therapy basic research is still far from providing the tools for the treatment of the previously mentioned illnesses. The most pressing issue that the field of gene therapy has to address is the development of efficient in vivo gene delivery systems. The in vivo administration of either functional genes or therapeutic factors would greatly simplify and improve any human gene therapy intervention." In the instant case, the specification does not provide guidance as to how any viral vector encoding for any of the claimed dnPLB molecules will be directed to specifically to cardiac myocytes and whether sufficient amount of dnPLB molecule could be produced to accelerate SERCA2 mediated calcium ion transport in the treated myocytes to improve cardiac muscle contractility. Furthermore, the specification does not provide any guidance as to what doses of a viral vector will be administered to target a viral vector to cardiac myocytes. While applicant's specification supports efficient in vivo cardiac

gene transfer by injecting dnPLB adenovirus (carrying val49ala mutation) into 1 day old neonatal mouse heart, and myocytes isolated 4 weeks after injection into the mouse heart an cell shortening was measured (example 3), the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting, levels of expression of a therapeutic dnPLB ptorein necessary to provide therapy and mode of administration of the therapeutic gene. These issues are noted by experts in the field of gene therapy and Verma et al, (Nature, 389: 239-242, 1997) noted that as of 1997, "there is still no single outcome that we can point to as a success story" (p 239, 1st column, 2nd paragraph). The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (p 239, 3rd column, 2nd paragraph). Moreover, applicant's claims do not recite any any particular mode of administration of a therapeutic dnPLB gene or a means to target cardiac muscle tissue with a therapeutic gene. It should be noted that although the publications date of these cited references are a year prior to the filing date of the instant application during the filing date and post-filing date of the instant application, the issues regarding the unpredictability of gene therapy remain the same and have not been resolved by the guidance provided by the instant specification.

In light of the above, it appears that the state of the art is suggesting that dnPLB gene therapy is unpredictable and lack of evidence of a method of treating any condition associated with loss of cardiac muscle contractility with any dnPLB gene. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of dnPLB gene therapy raised by the art. Therefore, the skilled artisan would conclude that the state of the art of dnPLB gene therapy is undeveloped and unpredictable at best. Given the lack of guidance provided the instant specification, it would have required undue experimentation to practice the invention as claimed for treating conditions associated

with loss of cardiac muscle contractility by dnPLB gene therapy without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of a condition associated with loss of cardiac muscle contractility, the lack of direction or guidance provided by he specification for treatment of said condition, the absence of working examples that correlate to the treatment of said condition, the unpredictable state of the art with respect to gene therapy, and in particular dnPLB gene transfer in vivo to cardiac myocytes of the heart, the undeveloped state of the art pertaining to the treatment of said conditions, and the breadth of the claims directed to any condition associated with loss of cardiac muscle contractility, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

7. No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Patent Examiner
Art Unit 1632

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER